Review

The evolution of the adipose tissue: a neglected enigma

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Abstract

The complexity of the anatomical distribution and functions of adipose tissue (AT) has been rarely analyzed in an evolutive perspective. From yeast to man lipid droplets are stored mainly in the form of triglycerides in order to provide energy during periods when energy demands exceed caloric intake. This simple scenario is in agreement with the recent discovery of a highly conserved family of proteins for fat storage in both unicellular and multicellular organisms. However, the evolutionary history of organs such as the fat body in insects, playing a role in immunity and other functions besides energy storage and thermal insulation, and of differently distributed subtypes of AT in vertebrates is much less clear. These topics still await for a systematic investigation using up-to-date technologies and approaches that would provide information useful for understanding the role of different AT subtypes in normal/physiological conditions or in metabolic pathologies of humans.

Kewwords:

1.Introduction

In recent years the simplistic vision of the adipose tissue (AT) as a component mainly devoted to energy storage and thermal insulation has been replaced by a more comprehensive evaluation of the complex physiology of AT, nowadays known for being involved in a variety of functions, such as immune responses and inflammation, reproduction and metabolism. The roots of such a complexity should be found in the evolution of AT. However, even though a better knowledge of the evolutionary history of the adipose tissue could be of help in understanding the distant causes of the adipose tissue-related pathologies in humans, this topic has been rarely conceptualized in evolutive terms [[1]]. The aim of our contribution is to gather data and observations, in order to fix the basic events of the evolution of the AT. We conclude that further investigations are urgently needed in order to fill several gaps of knowledge that at present leave many empty spots in the puzzle of the evolution of the AT.

2. The organization of AT

The majority of the information on the AT organization derives from investigations in mammals in which two types of AT, namely white and brown adipose tissue (WAT, BAT), with different functions have been described [[2]]. WAT is characterized by adipocytes in which lipid droplets fuses in a large unilocular lipid droplet, and are stored for future necessities. BAT, is characterized by adipocytes with multilocular lipid droplets and is used for generating heat. Notably, at present BAT has been reported only in mammals [[3]] and therefore, unless specified, in this article AT will be considered as synonym of WAT.

AT-derived molecules represent an important source of energy, and are stored in the form of triglycerides. Energy sources introduced as glucids can be accumulated as glycogen or can also be converted to triglycerides and transferred to AT for storage. The adipocyte, the principal cell of AT, contains lipid droplets characterized by triglycerides in which the triglyceride lipase can hydrolyze the triglycerides to glycerol and fatty acids [[4]]. The latter can move

from adipocytes to blood with the help of specific carriers reaching other tissues where they are used as energy source [[5]]. As it is well-known in mammals, the triglyceride lipase action is inhibited by insulin [[6]].

The ability to store nutrients, mainly in the form of triglyceride (triacylglycerol, TAG or triacylglyceride), necessary to provide energy during periods when energy demands exceed caloric intake, is a basic life function and, not surprisingly it is already present in unicellular organisms. Kadereit et al. [[7]] reported on the evolutionary conservation of those genes that are involved in the capacity of storing TAG from yeast to man.

The AT is not only involved in the uptake, storage and release of lipids, but also plays important role as endocrine organ, and is involved in immune-neuroendocrine response (Fig. 1).

3. WAT as an endocrine organ

In humans, WAT is considered an endocrine structure in which the adipocytes secrete several humoral factors, including adipokines (leptin, adiponectin, resistin, adipsin and visfatin), cytokines (IL-6 and TNF-α) and acylation-stimulatin protein (ASP) that have local, peripheral and central effects [[8]-[10]]. Leptin plays a pivotal role in energy homeostasis by decreasing food intake and increasing energy expenditure [[8]-[11]]. Furthermore, it intervenes in high-energy-demanding processes such as immune and neuroendocrine functions [[11], [12]]. Leptin was also found in the carp *Cyprinus carpio*, in the frog *Xenopus laevis*, in the chicken *Gallus gallus domesticus*, in fast-moving reptiles and non-human mammals [[3]]. In both human and mice, leptin circulating levels present similar oscillations in relation to meal timing (Stofkova, 2009). Functions leptin con eventuali differenze fra le specie The adipokine adiponectin is involved in regulating the sensitivity of AT to insulin, and its effects may vary on the basis of the isoform considered [13]. Conversely, the cysteine-rich protein resistin seems to intervene in promoting obesity and in the development of insulin resistance [14], even though several other physiological functions have been proposed [15]. Adipsin is equivalent to complement factor

D suggesting a role of AT in immune functions [16]. Visfatin binds and activates the insulin receptors, exerting insulin-mimetic effects [17]. ASP modulates the rate at which fatty acids are taken up and converted to triglycerides by adipocytes and interacts in a variety of pathways that involve energy storage and release [18].

4. AT and immune-neuroendocrine response

AT is also an active participant in the immune response and inflammation by mean of the two cellular components of the tissue, *i.e.*, adipocytes and macrophages. The first, intervene by producing several immune molecules such the pro-inflammatory cytokines IL-6 and TNF-α, and the adipokines. The strong correlation between AT and immune system is also documented by the presence of Toll-like receptors in adipocytes and in inflammatory conditions it can be observed that adipokines, such as leptin, enhance diapedesis of blood monocytes [19], [20] stimulate proliferation and phagocytic activity of monocytes/macrophages, chemotaxis of neutrophils and the synthesis of oxygen radicals [13]. Together with its participation in innate immunity, leptin affects neuroendocrine system through the decrease in orexigenic peptides such as neuropeptide Y (NPY). NPY is a neuropeptide that plays a key role in the hypothalamic regulation of energy balance and metabolism [21] and in increasing anorexigenic peptides, such as corticotrophin-releasing hormone (CRH) and α-melanocyte-stimulating hormone (α-MSH). Insulin, glucocorticoids and cytokines acting on the adipose tissue induce the release of leptin that, in turn, acts on the immune and neuroendocrine systems [22]. Also for other adipokines a possible influence on immune-neuroendocrine response has been proposed in non-patological situations. The role of adiponectin in regulating the energy homeostasis at hypothalamic level is still debated [13], whereas for resistin it has been proposed a role on the hypothalamic anorexigenic pathway similar to that described for leptin [15].

Presence of lipid droplets in yeast and pluricellular organisms

As in other eukaryotes, the yeast *Saccharomyces cerevisiae* synthesizes TAG and steryl esters thus forming the core of the so-called lipid particles, also known as lipid droplets or lipid bodies. Three lipases are involved in TAG catabolism of *S. cerevisiae* [23], [24]. Similar enzymes were detected in another yeast species, *Candida parapsilosis*, [25], in the insect *Drosophila melanogaster* [26], in mammalian cells [27] and even in the plant *Arabidopsis thaliana* [28].

TAG are present in the pseudocoelomate nematode *Caenorhabditis elegans* and they are stored in form of lipid droplets in the intestinal epithelial cells and in the yolk of gametes. The energy supplied by TAG is used during embryogenesis, when there is little food available and during non-feeding dauer stage. *C. elegans* fatty acids are obtained from either the food (*i.e.*, bacteria) or *de novo* through acetyl CoA [29] [30].

In molluscs, an invertebrate group characterized by a soft body often protected by a shell that evolved more that 500 million years ago [31], neutral and polar lipids were found in the soft tissues of the sea snail *Ifremeria nautilei* [32] where TAG represents the principal lipid component. A different pattern was reported in the green abalone *Haliotis fulgens* where a low level of neutral lipids was found [33]. The fatty acids profile of *H. fulgens* is similar to that observed for the foot muscle of other abalones such as *Haliotis laevigata* and *Haliotis rubra*, respectively [34]. The *H. fulgens* hepatopancreas, an organ also known as digestive gland, which exerts both absorption and secretive activities, is the site of lipid storage. The lipid composition in this gland is related to the diet and temperature and it is interesting to note that in the green abalone lipids seem to be primarily utilized for growth and gonad maturation, rather then as energy source [33]. Distinct neutral lipids were detected in digestive gland and gonad of the freshwater snail *Helisoma trivolvis* infected by four larval species of trematodes, and in particular, elevated levels of TAG were observed [35].

Several insects are active consumer of lipids that are mainly stored in the fat body. This organ is also involved in different humoral functions including nutrition, reproduction, longevity, production of antimicrobial peptides, among others [36][38]. Usually, neutral lipids are stored as TAG, but in the hemolymph

of numerous and evolutionary distant insect taxa, such as locusts, silkmoths, cockroaches, bugs, etc. lipids are released as diglycerides [39]. The synthesis of diglycerides and triglycerides by the fat body of insects seems to follow the same pathway observed in vertebrates [40] whereas fatty acids are broken down via β-oxidation [41].

Among deuterostomian invertebrates, the fatty acid composition was determined by gas-liquid chromatography in various echinoderms, such as the sea star *Asterias rubens*, the sea urchin *Echinus esculentus* and the sea cucumber *Holothuria forskali* [42]. These animals introduce lipids via their diet and the type of diet affects the composition of fatty acid, as observed in the gonad of the sea urchin *Psammechinus miliaris* [43].

In lampreys, *i.e.*, ~~one of the most primitive species of the~~ a present-day vertebrate~~s~~ with several plesiomorphic characters, it seems possible to glimpse the presence of fat cells that could be ascribed to the typical cells of the AT. Indeed, Müller [44] described the presence of cells with morphological characteristics comparable with those of WAT and BAT adipocytes in the perimeningeal tissue of lampreys. It is worth noting that in subsequent studies the term AT has been used in the lamprey *Petromyzon marinus* [45] [46]. As reported by Müller [44] the presence in lampreys of adipocytes with characteristics comparable to those of BAT adipocytes is in contradiction with opinions already present in literature and recently reaffirmed. Indeed, it is generally accepted that BAT is not present in cold-blooded vertebrates, while WAT has been detected in the majority of vertebrate taxa, including fish, amphibians, reptiles and mammals [[3], [47][48].

On the distribution of lipid droplets and AT in invertebrates and vertebrates

The distribution of fat among both invertebrate and vertebrate groups is quite inhomogeneous. Pond [49] coined the term “Cinderella tissue”, as fat seems to be located in those spaces that remain unoccupied by other tissues. For instance, in distant and unrelated taxa like protostomian and

deuterostomian invertebrates, the lipid droplets are differently located in various organs on the basis of the taxon considered [[34], [39][42] [43]. Passing to vertebrates, in both anamniote and amniote tetrapods like amphibians and several reptiles the AT is mainly stored in the intra-abdominal regions. In birds and mammals, that independently evolved homeothermy, AT is also retrievable in subcutaneous districts, a probable consequence of convergent evolution finalized to thermal insulation [[3]]. However, this assumption is partially questioned by the data reported by Pond [49] which found a similar distribution of subcutaneous AT in mammals living either in the tropical or arctic regions.

Conclusive remarks: evolutionary conundrums and perspective for human health and pathologies

The data summarized above, clearly indicate that in multicellular organisms the stored fat plays several different roles beside being a primary source of energy. However, this seems the only ~~real~~ easy certainty as it is ~~impossible~~ harder to ~~answer~~ tackle further ~~fundamental~~ questions such as ~~the three~~ those that follow. First, ~~is it possible~~ how to follow/describe the evolution of AT? In this context, it is worth mentioning that the development of vertebrate adipocyte presents some specificities. It is well-known that in triblastic organisms connective tissue cells derive from the mesenchymal progenitor cells, but surprisingly Billon et al. [50] found that adipocytes derive from neural crest, an element that can be retrieved exclusively in vertebrate development. In this perspective, when utilizing the term AT in vertebrate and invertebrate taxa, are we speaking of homologue structures? Or we are just referring to different components similarly devoted to lipid storage? While comparing vertebrate anatomical components with their invertebrate counterparts, it should be remembered that two whole genome duplications occurred at the base of vertebrates. It has been observed that this event attributed some unique functional and structural features to the vertebrate tissues [51]. This let the real homology between vertebrate WAT and invertebrate lipid storages a subject open to debate. ~~Second, can we properly use the term AT in invertebrates? Third,~~ Can the distribution/organization of lipid droplets and AT be used as a

character for phylogeny-related studies? ~~parameter for evolutionary speculations~~?

Despite ~~the lack of~~ at present it is not easy to establish an answer~~s~~ to the ~~three~~ above mentioned questions, a recent study showed the presence of a conserved family of genes that encode for proteins involved in the process of lipid storage ~~from yeast to humans~~ [[7]]. These proteins were called fat-inducing transcript (FIT), and are exclusively located in endoplasmic reticulum. Through a BLAST search, the authors have found out orthologs of the mammalian *FIT1* and *FIT2* in several invertebrate and vertebrate taxa. More in detail, one *FIT* gene ortholog to *FIT2* has been identified in worms, insects, amphibians and birds. Two *FIT2* orthologs were identified in *S. cerevisiae*, while in the zebrafish *Danio rerio* one ortholog for *FIT1* and another for *FIT2* were found. As a consequence, the evolution of lipid storage and distribution exploited a tight conservation of its molecular basis. On the other hand, some vertebrate specificities can be retrieved also at molecular level. Cide family proteins modulate several metabolic processes in vertebrates, including lipolysis, lipogenesis and TAG storage in WAT and BAT. A comparative genomic analysis demonstrate that while CIDE-N domain is distributed and conserved among metazoans, whereas CIDE-C domain exists only in vertebrate. As a consequence, the CIDE protein family members, together with their specific role on lipid metabolism, can be retrieved only in vertebrates [52].

On the whole, present knowledge allow to conclude that molecular basis of lipid metabolism are in general conserved, but at ~~However, while at molecular level the conservation is remarkable,~~ at tissue level variability and divergence seem to represent the rule.

The interest for evolutive aspects of fat tissue is not only related to cultural aspects. An open question in humans is the ancestral basis of the body distribution and biological function of AT, and its physiopathology. Different types of AT are present in humans, such as BAT and WAT, and the latter can be further subdivided into subcutaneous, visceral, mediastinic, pericardial and intramuscular, among others [[1]]. The differences between these anatomically differently distributed subtypes of AT have not been systematically investigated

from an evolutionary point of view using up-to-date technologies and approaches (gene expression profiling, miRNA profiling, whole genome epigenetic studies, among others). Future studies should address such topics either in normal/physiological conditions (development and healthy aging) or in metabolic pathologies (obesity, metabolic syndrome and diabetes) where a complex balance between different subtypes of AT can occur, and where some of them can represent risk factors while others can play an (opposite) beneficial role [53].

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Figure legend

Fig. 1 Schematic drawing of the mammalian adipocyte secreting adipokines (leptin, adiponectin, resistin, adipsin, visfatin), cytokines (IL-6, TNF-α) and acylation-stimulatin protein (ASP), and its other related functions.